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Thiazolidinediones and fluid retention

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CASE PRESENTATION

A 67-year-old Caucasian woman was admitted to our hospital with progressive shortness of breath and swelling of all four extremities. Her past medical history included type 2 diabetes and hypertension of approximately 20 and 10 years of duration, respectively, hypothyroidism, morbid obesity, paroxysmal atrial fibrillation, and sciatica. She denied a history of diabetic nephropathy or retinopathy. On questioning, she noted that over the previous 4 months she had developed new onset of lower extremity edema, increasing abdominal girth, and approximately 60 lb weight gain. More recently over the 3 weeks before admission, she had developed new onset of orthopnea and dyspnea with minimal exertion. She denied any recent history of chest pain, fever, foamy urine, or leg pain. Medications at the time of admission included lopressor 50 mg daily, lisinopril 10 mg daily, hydrochlorothiazide 50 mg daily, furosemide 40 mg daily, repaglinide 2 mg daily, rosiglitazone 8 mg daily, gabapentin 200 mg twice daily, and levothyroxine 200 μg daily. Except for the gabapentin, which had been added 3 weeks before admission for her sciatica, she had been on stable dosing of her other medications for the previous several months. Rosiglitazone had been added approximately 36 months before the current presentation. The prescribing physician had not recorded a baseline weight at that time. She had not been treated with insulin for her diabetes, and she had not taken any non-steroidal anti-inflammatory agents in the previous few months. Pulse oximetry revealed an oxygen saturation of 90% while breathing room air, which increased to 100% while breathing supplemental oxygen at a rate of 2 l/min. She was afebrile, and her blood pressure was 120/70 mm Hg. On examination, she was anxious, visibly short of breath, and unable to complete full sentences. She was markedly obese. She had crackles in both lung fields up to the apices. She had deep pitting edema of the arms, legs, anterior abdominal wall, and pre-sacral areas. Heart sounds were distant. Examination of the head and neck, skin, and joints and lymph nodes was unremarkable. Electrocardiogram showed sinus tachycardia at a rate of 100 bpm. Portable chest X-ray (CXR) showed cardiomegaly and perihilar edema consistent with congestive heart failure (Figure 1). Ultrasound of the lower extremities showed no evidence of deep venous thrombosis and a ventilation-perfusion (V/Q) scan showed no evidence of pulmonary embolism. Patient laboratory data are indicated in Table 1.

HOSPITAL COURSE AND CLINICAL FOLLOW-UP

She was admitted with a diagnosis of new onset of congestive heart failure (CHF) and was started on intravenous furosemide 40 mg twice a day. Transthoracic echogram was non-diagnostic due to the patient's body habitus and poor acoustic penetration. Transesophageal echocardiogram showed mild left ventricular hypertrophy, normal left ventricular systolic function, and impaired mitral filling consistent with diastolic dysfunction. Right heart catheterization was performed (Table 2). The etiology of the patient's biventricular pressure/volume overload was not immediately apparent. Thiazoledinedione-induced fluid retention was considered, and hence rosiglitazone was discontinued. Neseritide was added as a continuous infusion at a rate of 0.01 μg/kg/min to enhance natriuresis in the setting of elevated pulmonary capillary wedge pressure with preserved left ventricular systolic function. In addition, spironolactone was started at 25 mg twice daily. She sustained a net negative fluid balance of approximately 1.5 kg/day, with improvement in symptoms. Neseritide was discontinued after 5 days. She was discharged home on the tenth hospital day, having lost 15 kg since admission. Medications at the time of discharge included furosemide 40 mg p.o. twice daily, spironolactone 25 mg p.o. twice daily, acetazolamide 250 mg p.o. twice daily (added because of the development of mild metabolic alkalosis), metoprolol XL 50 mg p.o. twice daily, levothyroxine 200 μg p.o. twice daily, and repaglinide 1 mg p.o. twice daily. Acetazolamide was stopped three weeks after hospital discharge. During subsequent clinic follow-up visits, she was noted to experience ongoing weight loss and resolution of her edema. At the 4-month mark following the initial diagnosis of CHF, her weight had decreased by 54 kg (from the admission weight of 142 kg down to 88 kg).

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CLINICAL DIAGNOSIS

Rosiglitazone-induced fluid retention leading to biventricular pressure and volume overload, CHF, and anasarca.

DISCUSSION

In this complex patient with new onset of symptomatic CHF, one has to consider a broad differential diagnosis. The patient had several risk factors predisposing to diastolic dysfunction, including long-standing hypertension, obesity, and type 2 diabetes. The development of her symptoms cannot be attributed to myocardial ischemia or myocarditis, given the absence of chest pain or abnormal electrocardiogram findings, normal troponin levels, and predominantly diastolic dysfunction with absence of segmental wall motion abnormalities on transesophageal echocardiogram. There was also no evidence of significant valvular disease or pericardial disease. Metabolic causes, such as hemochromatosis or amyloidosis, were also unlikely given the absence of other clinical factors. Because of her obesity, the patient was at high risk for obstructive sleep apnea, which potentially could have contributed to her hypertension and heart failure. Although a formal sleep study has never been performed, the fact that her symptoms resolved without specific sleep apnea therapy supports the exclusion of this cause. She also denied using non-steroidal anti-inflammatory drugs and has not been treated with calcium channel blockers before admission. Although mild weight gain and lower extremity edema have been previously reported with gabapentin use,[1] there are no reports of CHF, pulmonary edema, or fluid retention with this medication. The patient had a history of mild anemia with normal iron, B_{12}, and folate levels. The pattern of hemoglobin change over time (Table 1) is consistent with hemodilution from massive volume retention. Within 4 months of stopping rosiglitazone and with resolution of CHF, her hemoglobin had normalized without iron or erythropoietin therapy. The temporal sequence of events points to a long-standing thiazolidinedione (TZD)-induced fluid retention as the most likely cause of this patient's presentation. Although the time course for development of symptomatic CHF in this patient since initiation of rosiglitazone (approximately 3 years) is longer than reported in most other studies, a thorough clinical evaluation upon hospitalization was unable to identify any other likely causative factor(s) to explain this patient's marked fluid retention and CHF. This causal relationship is further supported by the swift resolution of the patient's symptoms after discontinuation of rosiglitazone therapy, and maintenance of a stable weight on long-term follow up. We postulate that the process of gradual fluid retention was

Figure 1 | Portable AP view of the chest demonstrates cardiomegaly, perihilar edema, and blunting of the left costophrenic angle, consistent with congestive heart failure.

Table 1 | Laboratory results

Test	4 months before admission	Date of admission	4 months after discharge	Reference range
Blood urea nitrogen (mg/dl)	17	38	18	7–20
Creatinine (mg/dl)	0.6	1.2	0.7	0.5–0.9
WBC (10^9/l)		6.0		3.5–9.0
Hemoglobin (g/dl)	10.7	8.8	12.1	12.0–15.0
Platelet (10^9/l)		217		165–415
Albumin (g/dl)	3.7	3.8		4.0–5.0
Cholesterol (mg/dl)		164		<200
TSH (μU/ml)		5.38		0.3-4.2
BNP (pg/ml)		338	72	<100
Fe (μg/dl)	46	46		41–141
TIBC (μg/dl)	327	422		251–406
Ferritin (ng/ml)	94	49		10–150
B_{12} (pg/ml)	1522			279–996
Folate (ng/ml)	19			5.4–18.0
Spot urine protein (mg/dl)		24		
Spot urine creatinine (mg/dl)		132		
Troponin		Normal $\times$ 3 over 24 h		
Urine dipstick		Negative for protein or blood		
Urine microscopy		No hematuria or pyuria		

BNP, brain natriuretic peptide; TSH, thyroid-stimulating hormone; WBC, white blood cells.

Table 2 | Right heart catheterization data

Measurements	Value	Normal values
Right atrium (mm Hg)	27	0–6
Pulmonary artery (mm Hg)	65/35	25/10
Pulmonary capillary wedge pressure (mm Hg)	28	8–12
Cardiac output (l/min)	5.53	4.0–8.0
Cardiac index (l/min/m^2)	2.76	2.5–4.0
Mixed venous oxygen saturation (%)	66	60–75

probably facilitated by the patient's background physiology of diastolic dysfunction from hypertension, and possibly sleep apnea.

The goal of this report is to review the recently discovered mechanisms of TZD-induced edema and to relate these discoveries to clinical practice. We will begin by briefly reviewing the clinical use of TZDs and their peroxisome proliferator-activated receptor (PPAR)-mediated effects.

Clinical use of TZDs

TZDs are widely used to treat type II diabetes. Their mechanism of action is attributed to binding and activation of the PPAR-γ. Three drugs in this class have been studied extensively in humans: troglitazone, rosiglitazone, and pioglitazone. Troglitazone was approved in the United States in January 1997 as the first PPAR-γ agonist for treatment of type 2 diabetes. The approval of rosiglitazone and pioglitazone followed in 1999. Troglitazone was withdrawn from the market in March 2000, because of reports of liver toxicity. Hepatotoxicity associated with rosiglitazone and pioglitazone is rare, and these drugs are currently in widespread clinical use worldwide. Both drugs at maximal doses lead to an absolute decrease in glycosylated hemoglobin of approximately 1–1.5%.[2] Given the often suboptimal results from the use of other oral glucose-lowering agents alone or in combination, the use of TZDs has been increasing steadily. In addition, the recent publication of the DREAM trail (The Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) is likely to extend the use of TZDs to the pre-diabetic population. In this large, prospective, randomized, international controlled trail, rosiglitazone at 8 mg daily for 3 years significantly reduced the incidence of new onset of type II diabetes in adults with impaired fasting glucose or impaired glucose tolerance.[3] Fluid retention, as illustrated by our case, is the most serious potential side effect of currently available TZDs.

TZDs and PPARs

PPARs are recently discovered nuclear transcription factors essential to the control of energy metabolism that are modulated via binding with tissue-specific fatty acid metabolites.[2] Of the three PPAR isoforms, α and γ have been extensively studied. Less is known about PPAR-δ. PPAR-α is predominantly found in liver, muscle, and vascular endothelial cells. PPAR-γ is expressed at high levels in adipose and liver tissues, macrophages, and pancreatic-β cells. PPAR-γ exerts its biologic effects via the processes of transactivation or transrepression. In transactivation, PPAR-γ interacts with the retinoid X receptor within the cell nucleus; following tissue-specific ligand activation, this leads to the regulation of target genes via interaction with specific DNA promoter regions, termed PPAR response elements. In transrepression, ligand binding with PPAR-γ leads to direct inhibition of signal transduction pathways in a DNA binding-independent manner. Multiple biologic pathways have been demonstrated to be influenced by PPAR-γ stimulation. Beyond the metabolic syndrome, TZDs have been proposed as potential therapeutic modulators of atherosclerosis,[4] sepsis and inflammation,[5] cancer,[6] non-alcoholic fatty liver disease,[7] polycystic ovarian syndrome,[8] and HIV-associated lipodystrophy.[9] PPAR-γ stimulation results in increased glucose transport in target tissues, as well as enhanced insulin sensitivity in liver and adipose tissue leading to decreased release of glucose and free fatty acids into the circulation. Troglitazone and rosiglitazone are pure PPAR-γ agonists, whereas pioglitazone is primarily a PPAR-γ agonist and has some PPAR-α activity as well. Fibric acid derivatives, such as gemfibrozil and fenofibrate, exert their lipid-lowering effect via PPAR-α activation. Muraglitazar, a combined PPAR-α and -γ agonist, has been under active investigation. However, a recently published pooled analysis of clinical experience with this agent suggests that it carries an excessive risk of cardiovascular events.[10] Currently available PPAR agonists and their targets are summarized in Table 3.

TZDs and fluid retention

Weight gain of 1–3 kg is common in patients taking long-term TZDs when used alone or in combination with other oral glucose-lowering agents. Greater weight gains of 4–5 kg may be seen, however, when TZDs are used in combination with insulin therapy. Although a portion of the weight gain may be related to a redistribution of body fat stores from visceral to subcutaneous areas, the majority is probably the result of renal-mediated fluid retention, leading to an increase in plasma volume of approximately 1.8 ml/kg.[11] This increase in plasma volume may be accompanied by a mild dilutional anemia, and in some patients, the development of pedal edema or overt symptoms of CHF. Clinical studies have shown that edema develops in approximately 3–5% of patients taking TZDs, with the incidence increasing to 10–15% in those receiving concurrent insulin therapy. This heightened susceptibility to the development of weight gain and edema has been attributed to the fact that insulin-requiring patients tend to be older and have a greater incidence of microalbuminuria, coronary artery disease, and left ventricular hypertrophy, all conditions which may be associated with fluid retention.

Early clinical data suggested a relatively low incidence of CHF ($\sim$1%) in patients treated with TZD monotherapy, increasing 2–3% in those patients receiving insulin in addition to a TZD. Soon after the introduction of TZDs

into clinical practice in the late 1990s, however, multiple case reports appeared suggesting a possible causal link between TZD use and new onset CHF (reviewed by Nesto *et al.*[11]). Weight gain, edema, and CHF with TZD use appear to be both dose- and time-dependent. Case reports have described the development of CHF as early as 1 month after TZD initiation, and up to 12 months later. Subclinical development of CHF may be difficult to appreciate by history and exam, and some investigators have suggested the possible utility of serial brain natriuretic peptide monitoring during TZD treatment as a means of detecting early, asymptomatic CHF.[12]

Several large, retrospective analyses have yielded conflicting results regarding whether TZD use independently predicts index hospitalization for CHF.[13–15] Nevertheless, the American Heart Association and the American Diabetes Association published a joint consensus statement on TZD use and the risk of development of CHF in 2003.[11] The major recommendations included the following: (1) that TZD use should be avoided in patients with pre-existing New York Heart Association (NYHA) class III or IV CHF; (2) that the medications should be initiated at the lowest dose possible in patients with established NYHA class I or II CHF, asymptomatic left ventricular dysfunction, or at least one other risk factor besides diabetes for CHF; (3) that patients should be monitored carefully for evidence of weight gain or edema, and dose escalation should be performed gradually. Concurrent insulin treatment, although included as a risk factor for fluid retention, was not contraindicated by the joint committee. Risk factors for heart failure in diabetics treated with TZDs are summarized in Table 4.

Mechanism of fluid retention

Until recently, the mechanism by which TZDs cause fluid retention has been obscure. It had been speculated that multiple factors, such as arterial vasodilation, endothelial permeability, and renal Na^+ reabsorption contributed to this effect. Nearly a decade ago, Guan *et al.*[16] determined the localization of PPARs within the kidney. *In situ* hybridization revealed that PPAR-α mRNA was expressed in the proximal tubule and the medullary thick ascending limb, whereas PPAR-γ was expressed exclusively in the medullary collecting duct. Because the collecting duct plays a critical role in the regulation of sodium balance, this finding was highly suggestive of a PPAR-γ-mediated contribution to distal sodium reabsorption.

PPAR-γ and the sgk1–Nedd4-2–ENaC pathway

Expression and activity of the epithelial sodium channel (ENaC) constitute the rate-limiting step for Na^+ transport across the collecting duct epithelium. ENaC is localized at the apical cell membrane of the principal cell within the collecting duct of the distal nephron. Its synthesis and activity are regulated by aldosterone in response to fluctuations in effective arterial blood volume and activation of the renin–angiotensin–aldosterone axis. It is composed of three subunits, designated ENaC-α, -β, and -γ.[17] Maintenance of electroneutrality during sodium transport across the collecting duct epithelium is made possible by potassium secretion into the tubular lumen via the renal outer medullary K channel, which is also under the effect of aldosterone. The central role of ENaC in the maintenance of Na^+ balance is exemplified by certain forms of hereditary hypertension, such as Liddle's syndrome. The study of this syndrome led to the discovery of the ENaC regulatory pathway and has contributed to our understanding of the molecular mechanisms of Na^+ and volume homeostasis. Liddle's syndrome is a monogenic disorder, which results from mutations in the PY motif of the ENaC-α or -γ subunits. Normally the PY motif interacts with the ubiquitin ligase Nedd4-2, leading to endocytosis and degradation of the ENaC complex. Mutations within the PY motif result in the ENaC complex being protected from inactivation, resulting in constitutive Na^+ reabsorption and volume-dependent hypertension. Several proteins interact with or modify Nedd4-2 function. One of them, the serum- and glucocorticoid-inducible kinase 1 (sgk1) is of special interest as it appears to be regulated by both aldosterone and insulin.[18]

Table 3 | PPAR isoforms, expression sites, and available agonists[2]

Receptor:	Expression sites	Agonist effect	Available agonists
PPAR-α	Main sites: liver and skeletal muscle. Other: heart muscle, vascular smooth muscle, and endothelium	Lipid-lowering effect, increased fatty acid uptake and catabolism, anti-inflammatory effect, prevent or retard atherosclerosis in mice and humans	Fenofibrate Bezafibrate Ciprofibrate Gemfibrozil
PPAR-γ	Main site: adipose tissue. Other: renal medullary collecting ducts, endothelium, pancreatic-β cells, and at low levels in muscle and liver cells	Increased insulin-dependant glucose uptake (insulin-sensitizing effect), increased fatty acid uptake and storage, increased adipocyte differentiation, increased subcutaneous adipose tissue mass, decreased iNOS, increased collecting duct ENaC expression and Na^+ reabsorption	Troglitazone (pure γ action) Rosiglitazone (pure γ action) Pioglitazone (some α activity) Muraglitazar (dual α–γ agonist)
PPAR-delta	Skin, brain, adipose tissue, and at low level in multiple other tissues	Poorly defined	Experimental only

ENaC, epithelial sodium channel; iNOS, inducible nitric oxide synthase; PPAR, peroxisome proliferator-activated receptor.

Table 4 | Risk factors for heart failure in patients treated with TZDs[a]

1. History of systolic or diastolic heart failure
2. History of CAD
3. Hypertension
4. LVH
5. Aortic or mitral valvular disease
6. Advanced age (>70 years)
7. Long standing diabetes (>10 years)
8. Preexisting edema or loop diuretic therapy
9. Development of edema on TZD therapy
10. Insulin co-administration
11. Chronic kidney disease (Cr>2.0 mg/dl)

CAD, coronary artery disease; LVH, left ventricular hypertrophy; TZD, thiazolidinedione.
[a]Adapted from the AHA and ADA Joint Consensus Statement.[11]

Sgk1 is a member of the serine/threonine protein kinase family and is expressed in the distal nephron. Basal levels of sgk1 are maintained by glucocorticoids,[19] but aldosterone can rapidly stimulate sgk-1 mRNA expression.[20] After synthesis and activation by phosphorylation, sgk1 interacts with and inactivates Nedd4-2 by phosphorylation. In this way, Nedd4-2 is prevented from interacting with ENaC's PY motif, resulting in decreased ENaC degradation.[21] In addition, sgk1 stimulates the activity of basolateral Na^+K^+-ATPase,[22] thus facilitating Na^+ reabsorption at both apical and basolateral sites. In addition, sgk1 activation has been shown to be partly dependent on the insulin signaling pathway via the intermediate phosphatidylinositol 3-kinase and 3-phosphoinositide-dependent kinase. Specific phosphatidylinositol 3-kinase inhibition in renal cell lines prevents mineralocorticoid-induced sgk1 activation and subsequent ENaC-mediated Na^+ transport.[18] Sgk1 knockout mice are normotensive and demonstrate normal Na^+ balance on standard dietary Na^+ intake. In contrast, Na^+ deprivation unmasks their impaired ability to reabsorb Na^+ despite high serum aldosterone levels, resulting in volume depletion, hypotension, and decreased glomerular filtration rate.[23] The major elements of Sgk-1–Nedd4-2–ENaC pathway are illustrated in the left-hand panel of Figure 2.

The first report describing PPAR-γ interaction with this pathway came from Hong *et al.*[24] These authors demonstrated that sgk1 activity is stimulated by treatment of a human cortical collecting duct cell line with PPAR-γ agonists. The activity of sgk1 paralleled an increase in sgk1 mRNA and was followed by an increase in cell surface ENaC-α expression. This effect was abolished by pretreatment with a specific PPAR-γ antagonist. Electrophoretic mobility shift assay suggested that these effects were caused by binding of PPAR-γ to a specific response element within the sgk1 gene promoter. Therefore, it appeared that the gene for sgk1 is a direct target for PPAR-γ transactivation.

More recently, Guan *et al.*[25] used an alternative method to investigate the effect of PPAR-γ activation on ENaC expression. They utilized Cre-loxP recombination methodology to create mice with site-specific knockout of the PPAR-γ gene within the renal cortical collecting duct. Unlike wild-type controls, mice lacking PPAR-γ in the collecting duct did not increase their body weight after treatment with pioglitazone. Moreover, they demonstrated diminished sodium avidity compared to wild-type mice when placed on a low-salt diet, in spite of elevated basal aldosterone levels. Further experiments evaluating amiloride-sensitive Na^+ flux in cultured collecting duct cells confirmed that after *Cre*-mediated deletion of the PPAR-γ gene, Na^+ flux was no longer stimulated by pioglitazone. Moreover, the authors demonstrated that pioglitazone increased mRNA expression of the ENaC-γ subunit, which preceded the detectable increase in Na^+ flux. The increase in mRNA levels was not abolished by inhibition of protein synthesis with puromycin, which suggests that the ENaC-γ gene is a direct target activated by PPAR-γ, not dependant on the synthesis of other transcription factors. Prior studies showed that the expression of the γ-subunit is particularly important for trafficking and regulation of ENaC expression at the cell membrane.[26] Interestingly, in contrast to the study by Hong *et al.*, these authors did not find evidence for increased sgk mRNA expression in response to PPAR-γ activation. The illustration of the postulated PPAR-γ effects is provided in the right-hand panel of Figure 2.

Potential treatment strategies

The above findings suggest that targeted ENaC inhibition via direct receptor blockade (amiloride) or inhibition of channel synthesis and activity (spironolactone) may be particularly effective in preventing or treating TZD-induced edema. Interestingly, a recent study investigating the efficacy of different diuretic classes in patients who developed fluid retention in response to TZDs demonstrated that spironolactone in comparison with either furosemide or hydrochlorothiazide led to a greater diuretic response in patients who continued their TZD in spite of evidence of weight gain.[27] Outcome measures in this study included changes in weight, total body water, and extracellular fluid volume as determined by non-invasive bioelectrical impedance, and changes in hematocrit, as a surrogate marker for changes in plasma volume. Unfortunately, these investigators did not include amiloride, a specific ENaC blocker, as one of the treatment arms. In the mouse model, amiloride effectively prevents pioglitazone-induced fluid retention.[25] Although similar data with amiloride are lacking thus far in humans, such an approach is physiologically intuitive and may prove to be more useful than the use of loop diuretics acting within the thick ascending limb. Future clinical research may help confirm this hypothesis.

SUMMARY AND RECOMMENDATIONS

Recent discoveries indicate that PPAR-γ stimulation is important in the regulation of Na^+ balance. The endogenous activator(s) of PPAR-γ in the collecting duct remain unknown, but its pharmacologic agonists demonstrate a significant effect on sodium and volume homeostasis.

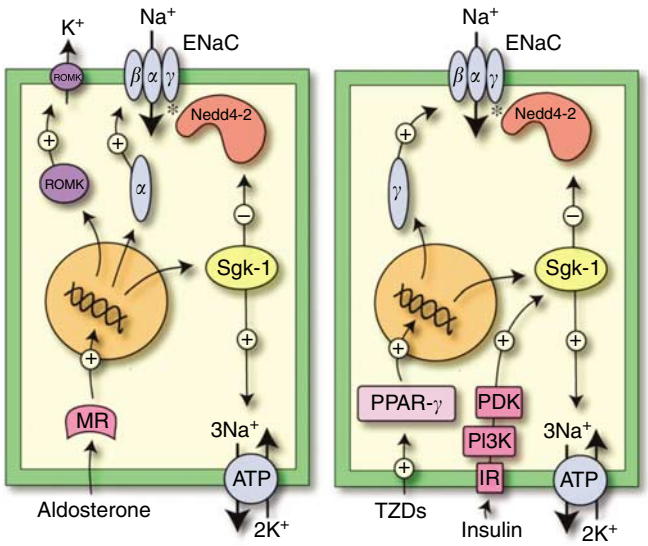

Figure 2 | Aldosterone and Sgk1–Nedd4-2–ENaC Pathway (left) and effects of PPAR-γ activation (right). Aldosterone interacts with its mineralocorticoid receptor (MR) and directly upregulates the mRNA levels of ROMK, ENaC-α, and Sgk-1. Sgk-1 inactivates Nedd4-2, stimulates basolateral Na^+K^+ ATP-ase, and activates ROMK (data not shown in this panel). The right panel illustrates a possible convergence point of the insulin and TZD-mediated pathways at Sgk-1 level. Thiazolidinediones (TZDs) activate PPAR-γ, which in turn increases the expression of ENaC-γ and inactive form of Sgk-1 (although not confirmed by Guan *et al.*). Insulin acts via phosphatidylinositol 3-kinase (PI3K) and phosphoinositide-dependant kinase (PDK) pathway which converts inactive Sgk-1 to its active form by phosphorylation. *the PY motif-mediated interaction between ENaC subunits and ubiquitin ligase Nedd4-2.

Whether the main effect of PPAR-γ agonists is mediated by transactivation of the genes encoding sgk-1, ENaC-γ, or both, remains uncertain. Although the clinically observed increased incidence of weight gain, edema, and CHF in patients on combined TZD/insulin therapy has been attributed to these patients generally having a greater number of traditional risk factors for development of CHF compared to non-insulin-treated patients, we have reviewed how the recently discovered synergistic interaction between the insulin signaling pathway and PPAR-γ-mediated sgk1 activation may, in part, account for this effect.

We recommend adherence to the guidelines put forward by the American Heart Association and the American Diabetes Association regarding initiation of TZD use in at-risk patients. Patients started on a TZD should be followed closely for weight gain or development of edema or symptoms of CHF. Clinicians understandably may be reluctant to discontinue TZDs if their use in specific patients is accompanied by significant improvement in glycemic control. Modest increases in weight not accompanied by symptomatic CHF potentially can be managed successfully by instituting a diuretic regimen specifically targeting ENaC-mediated sodium reabsorption (amiloride or spironolactone), without necessarily discontinuing the TZD. Significant weight gain or new onset/worsening CHF in TZD-treated patients should prompt discontinuation of the TZD and initiation of appropriately aggressive supportive measures.

UPDATE

The newly released meta-analysis of 42 randomized trails revealed that rosiglitazone was associated with a small but statistically significant risk of myocardial infarction (odds ratio (OR) 1.43 with 95% confidence interval (CI): 1.03–1.98) and with an increase in the risk of death from all cardiovascular causes of borderline significance (OR 1.64 with 95% CI: 0.98–2.74).[28] It is currently unclear if these adverse cardiovascular outcomes are in any way related to fluid retention and CHF in the rosiglitazone-treated patients. Since expansion of intravascular volume increases left ventricular stress and myocardial oxygen demand, it is theoretically possible that such a causal link exists. It is also unclear if this effect is specific to rosiglitazone, or if it represents a class effect of all PPAR-γ agonists. Until further data becomes available, clinicians must be aware of these potential risks and need to carefully consider alternative treatments in susceptible type 2 diabetics.

REFERENCES

1. Kanbay M, Kaya A, Bozalan R *et al.* Gabapentin indiced edema in a geriatric patient. *Clin Neuropharmacol* 2006; **29**: 186.
2. Yki-Jarvinen H. Thiazolidinediones. *New Engl J Med* 2004; **351**: 1106–1118.
3. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. The DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) trial investigators. *Lancet* 2006; **368**: 1096–1105.
4. Roberts AW, Thomas A, Rees A, Evans M. Peroxisome proliferator-activated receptor-gamma agonists in atherosclerosis: current evidence and future directions. *Curr Opin Lipidol* 2003; **14**: 567–573.
5. Zingarelli B, Cook J. Peroxisome proliferator-activated receptor gamma is a new therapeutic target in sepsis and inflammation. *Shock* 2005; **23**: 393–399.
6. Koeffler HP. Perosixome proliferators-activated receptor gamma and cancers. *Clin Cancer Res* 2003; **9**: 1–9.
7. Belfort R, Harrison SA, Brown K *et al.* A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *New Engl J Med* 2006; **355**: 2297–2307.
8. Baillargeon JP, Iuorno MJ, Nestler JE. Insulin sensitizers for polycystic ovarian syndrome. *Clin Obstet Gynecol* 2003; **46**: 325–340.
9. Hadigan C, Yawetz S, Thomas A *et al.* Metabolic effects of rosiglitazone in HIV lipodystrophy. *Ann Intern Med* 2004; **140**: 786–794.
10. Nissen SE, Wolski K, Topol EJ. Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus. *JAMA* 2005; **294**: 2581–2586.
11. Nesto RW, Bell D, Bonow RO *et al.* Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Circulation* 2003; **108**: 2941–2948.
12. El-Muayed M, Lavis VR, Safi HJ, Fuentes F. Use of glitazones in cardiac patients: a case for B-type natriuretic peptide monitoring? *Am J Cardiol* 2004; **93**: 600–602.
13. Karter AJ, Ahmed AT, Liu J *et al.* Pioglitazone initiation and subsequent hospitalization for congestive heart failure. *Diabet Med* 2005; **22**: 986–993.
14. Patel C, Wyne KL, McGuire DK. Thiazolidinediones, peripheral oedema and congestive heart failure: what is the evidence? *Diabetes Vascul Dis Res* 2005; **2**: 61–66.
15. Hartung DM, Touchette DR, Bultemeier NC, Haxby DG. Risk of hospitalization for heart failure associated with thiazolidinedione therapy: a Medicaid claims-based case-control study. *Pharmacotherapy* 2005; **25**: 1329–1336.
16. Guan Y, Zhang Y, Davis L, Breyer MD. Expression of peroxisome proliferator-activated receptors in urinary tract of rabbits and humans. *Am J Physiol* 1997; **273**: F1013–F1022.

17. Canessa CM, Schild L, Buell G *et al.* Amiloride-sensitive epithelial Na+ channel is made of three homologous subunits. *Nature* 1994; **367**: 463–467.
18. Wang J, Barbry P, Maiyar AC *et al.* SGK integrates insulin and mineralocorticoid regulation of epithelial sodium transport. *Am J Physiol Renal Physiol* 2001; **280**: F303–F313.
19. Alvarez de la RD, Coric T, Todorovic N *et al.* Distribution and regulation of expression of serum and glucocorticoid-induced kinase-1 in the rat kidney. *J Physiol* 2003; **551**: 455–466.
20. Chen SY, Bhargava A, Mastroberardino L *et al.* Epithelial sodium channel regulated by aldosterone-induced protein sgk. *Proc Natl Acad Sci USA* 1999; **96**: 2514–2519.
21. Verrey F, Loffing J, Zecevic M *et al.* SGK1: aldosterone-induced relay of Na+ transport regulation in distal kidney nephron cells. *Cell Physiol Biochem* 2003; **13**: 21–28.
22. Zecevic M, Heitzmann D, Camargo SM, Verrey F. SGK1 increases Na, K-ATP cell-surface expression and function in *Xenopus* laevis oocytes. *Pflugers Arch* 2004; **448**: 29–35.
23. Wulff P, Vallon V, Huang DY *et al.* Impaired renal Na(+) retention in the sgk1-knockout mouse. *J Clin Invest* 2002; **110**: 1263–1268.
24. Hong G, Lockhart A, Davis B *et al.* PPAR gamma activation enhances cell surface ENaC alpha via up-regulation of SGK1 in human collecting duct cells. *FASEB J* 2003; **17**: 1966–1968.
25. Guan Y, Hao C, Cha DR *et al.* Thiazolidinediones expand body fluid volume through PPARgamma stimulation of ENaC-mediated renal salt absorption. *Nat Med* 2005; **11**: 861–866.
26. Konstas AA, Korbmacher C. The gamma-subunit of ENaC is more important for channel surface expression than the beta-subunit. *Am J Physiol Cell Physiol* 2003; **284**: C447–C456.
27. Karalliedde J, Buckingham R, Starkie M *et al.* Effect of various diuretic treatments on rosiglitazone-induced fluid retention. *J Am Soc Nephrol* 2006; **17**: 3482–3490.
28. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New Engl J Med*, advance online publication, 21 May 2007 (DOI: 10.1056/NEJMoa072761).